REMARKS/ARGUMENTS

1. Status of the Claims

Claims 37, 39, 41, 42, 48-51, and 53 are currently pending. Claim 42 is canceled herein.

2. Support

Claims 37 and 53 have been amended to recite "and wherein the modified human 5T4 antigen is a peptide fragment between 5 and 25 amino acids in length." Support for this amendment may be found, *e.g.*, on page 5, lines 25 and 30-31, page 25, lines 28-32, and page 26, lines 1-3 and 16-25, and in Examples 10 and 11, and SEQ ID NOS: 5-17.

3. Summary of Interview

Applicants thank Examiners DiBrino and Chan for the courtesy of a telephonic interview with the undersigned, on July 10, 2007 to clarify the position set forth in the final Office Action mailed May 18, 2007 (hereinafter the Office Action) regarding formality issues in connection with the present specification and the Examiner's consideration of references submitted in an Information Disclosure Statement (IDS) mailed March 14, 2007.

It was agreed to submit a Substitute Specification and comparison copy to incorporate (1) corrections to the Examiner's objections in the Office Action, (2) other corrections noted in the specification (typos and Greek characters), and (3) the prior edits, including the insertion of SEQ ID NOs, hyperlinks, and related applications.

In addition, it was agreed to move the description of the figures from about page 42 to about page 10. Examiner Chan also requested that the "abbreviated" descriptions of the figures at about page 42 be deleted in favor of the "detailed" descriptions of the figures also

provided at about page 42. Furthermore, it was agreed that the figure descriptions be amended to correct formality issues.

A new title of invention was agreed upon, "Expression Vectors Comprising Nucleic Acid Sequences Encoding 5T4 Antigen."

Karen Dow confirmed that all reference copies requested by the Examiner in the Office Action mailed October 12, 2006 were in fact electronically filed with Applicant's Responses of February 20, 2007 and February 22, 2007. Examiner DiBrino indicated that she would double check the status of the electronic re-submission of references and would follow up with a telephone call to Karen Dow. Examiner DiBrino called Ms. Dow at 4:45 PM EST and indicated she had located the missing references and would send a copy of the IDS to Ms. Dow noting on it that the references crossed out had been previously considered. Examiner DiBrino requested a complete copy of reference BF submitted with an IDS filed March 14, 2007. A copy of reference BF (Johnson et al. (1981) American Journal of Reproductive Immunology 1:246-254) is respectfully submitted herewith.

4. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 37, 39, 41, 48-51, and 53 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to meet the written description and enablement requirements. Applicants respectfully traverse the present rejections for the reasons on the record and for the following reasons.

The Examiner argues that Applicants were not in the possession of the claimed expression vectors at the time of the invention. The Examiner uses the same arguments to also conclude that the claimed invention is not enabled. Applicants disagree.

In particular, the Examiner argues that the disclosure "does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera,

including an expression vector(s) comprising a nucleic acid sequence encoding a modified 5T4 antigen, said antigen that includes a polypeptide that has been truncated, extended or otherwise mutated, by amino acid insertion, deletion or substitution, such that it differs from any naturally occurring 5T4, variant or allele derived from any species." See the bottom of page 9 of the Office Action mailed May 18, 2007 (hereinafter referred to as the Office Action). The Examiner therefore concludes that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed. For the same reasons, the Examiner concludes that the claimed invention is not enabled.

Applicants point out that the claims - as now amended - are directed to a modified human 5T4 antigen that is a peptide fragment between 5 and 25 amino acids in length. As the Examiner points out, the specification defines a modified 5T4 antigen as a 5T4 polypeptide which has been truncated, extended, or otherwise mutated such that it differs from naturally-occurring 5T4. See specification at page 5, lines 22-26. The claims are now directed to modified human 5T4 antigen peptide fragments between 5 and 25 amino acids in length. Therefore, contrary to the Examiner's assertions, the claims are not directed to mutants, variants or alleles derived from any species, the claims are directed to human 5T4 peptide fragments which are between 5 and 25 amino acids in length.

The specification discloses 13 different human 5T4 peptide fragments (SEQ ID NOS: 5-17 and Examples 10 and 11) as well as 13 different murine 5T4 peptides (SEQ ID NOS: 18-27). These modified 5T4 peptides were identified through HLA ranking prediction algorithms known in the art. Examples 10 and 11 illustrate that by scanning the human, mouse, and canine 5T4, one could use publicly available algorithms to accurately and rapidly identify 5T4 modified peptides with enhanced efficacy.

It is also important to point out that the claimed vectors require that the 5T4 peptides are capable of inducing an anti-tumor immunotherapeutic response. This claim limitation is quite important in view of the state of the art which supports that HLA-peptide

binding and stability information is the most influential factor correlating to CTL responses. This point is illustrated by the numerous examples in which a similar publicly available HLA binding program (bimas HLA_bind) has been used to identify potential CTL epitopes that have been used to successfully induce anti-tumor CD8+ T cell responses (e.g., Overwijk et al. (1998) J. Exp. Med. 188(2):277-286; of record, see the Information Disclosure Statement (IDS) filed July 30, 2004, reference A72). Moreover, when previously identified CTL epitopes are screened, using the Parker HLA-peptide algorithm, they are found to be within the top 2% of ranked peptide binders (Parker et al. (1994) J. Immunol. 152:163-175; of record, see the IDS filed July 30, 2004, reference A31). Accordingly, the state of the art supports that peptide binding and stability prediction programs identify peptides having CTL-inducing capabilities.

The instant application describes, for the first time, the use of 5T4 as a viable candidate for tumor immunotherapy. Indeed, the gene based 5T4 approach, detailed in the specification, has been proven to break tolerance at both the antibody and T cell level without inducing auto immune pathology in late stage colorectal cancer patients. See Harrop et al. (2006) Clin. Cancer Res. 12(11):3416-3424 (enclosed herewith). Subsequent studies in the same indication have shown that the incidence of a 5T4 T cell response is statistically linked to clinical benefit. See Harrop et al. (2007) Clin. Cancer Res. 13(15):4487-4494 at page 4493, col. 1, para. 2, thus providing evidence that 5T4 CTL epitopes can be efficiently presented and are present on the surface of tumors, statistically linking 5T4 specific CTLs to providing a therapeutic effect (reference enclosed herewith). To date, several hundred patients, suffering from an array of cancer pathologies, have been vaccinated with the gene-based 5T4 approach, and a Phase III study in renal cancer is ongoing. For further information relating to these clinical trials see the assignee's website: http://www.oxfordbiomedica.co.uk.

In addition, Applicants would like to point out subsequent work disclosed in WO06/120473 (Oxford BioMedica). In this work, Applicants provide evidence that the peptides identified through publicly available algorithms are also candidate peptides identified through patient screening. See for example, peptides 49, 142, 151, 176, and 183 in WO06/120473 which

correspond to SEQ ID NOS: 5, 9, 17, 7, and 15 in the instant application. As the Examiner will note, peptide 49 (SEQ ID NO: 5) is confirmed to elicit a response in patient screening. See, for example, page 62 of WO06/120473.

The Examiner asserts that the state of the art is unpredictable in the absence of appropriate evidence that the claimed expression vectors can be made and/or used. Applicants disagree with this assertion because the appropriate evidence has been provided. The specification teaches the construction of vectors comprising 5T4 sequences. The state of the art supports that vectors expressing CTL peptides could be made and used for inducing T cell responses in mice. See Overwijk et al., *supra*. See also Hanke et al. (1998) J. Gen. Virol. 79:83-90 (enclosed herewith) who made and used vectors expressing human and murine class I epitopes derived from HIV. HLA peptide binding ranking programs were publicly available at the time of the claimed invention (i.e., Parker et al. www. Bimas.dcrt.nih.gov/cgi-bin/molbiol/ken_parker_comboform) and had been used to identify modified peptides with improved binding to MHC Class I (Overwijk et al., *supra*). Therefore, when armed with the specification and the state of the art, one of ordinary skill in the art would have been able to make and use vectors expressing modified 5T4 antigens comprising HLA CTL peptide epitopes with enhanced efficacy. Indeed, Harrop et al. (2007), *supra* support that there is a statistically significant relationship between induced 5T4 CD8+ CTL responses and clinical benefit in colorectal cancer patients.

The Examiner asserts that it would have required undue experimentation to determine which modified human 5T4 sequences differ from undisclosed naturally occurring 5T4 antigens. Applicants disagree. As discussed above, and as demonstrated in the specification, it was within ordinary skill to run the publicly available HLA binding algorithms against the human, murine and canine 5T4 antigens disclosed in the specification and identify modified 5T4 peptides with optimal binding characteristics for each available HLA CTL peptide epitope with enhanced efficacy. Furthermore, it is a routine technique to insert such sequences

encoding the identified modified peptides within vectors known in the art, e.g., see Overwijk et al. and Hanke et al., *supra.*

Indeed, the state of the art, for example, Overwijk et al., *supra* supports the concept of using tumor associated antigens (TAAs), from heterologous species, to identify Class I peptide sequences with minor modifications that result in the enhanced ability to bind and form stable complexes with MHC. Overwijk et al. also support that such results are linked to inducing more efficacious T cell responses. As the Examiner will note, the specification uses a similar MHC binding algorithm to Overwijk et al. Overwijk et al. identifies the human gp100 peptide that possessed enhanced binding to murine MHC (p281, col. 2, para. 2) and demonstrates that vector-based expression of the human gp100 9mer was able to induce CTLs that recognize murine gp100 target cells.

The Examiner asserts that additional factors are required to make a good HLA binding peptide into an effective inducer of CTL citing various references the Examiner calls evidentiary. However, the Examiner fails to cite any references which relate to vector-based immunotherapy or to 5T4-based immunotherapy. Accordingly, none of the references are applicable to the claimed invention or the state of the art relevant to the claimed invention. Moreover, Celis et al. (2002) J. Clin. Invest. 110(12):1765-1768, cited by the Examiner, support Applicants earlier point that publicly available algorithms can be used to enhance the design of effective peptide vaccines. See Celis et al., page 1767, col. 3, para. 2.

Accordingly, the written description and enablement rejections should be withdrawn.

5. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 37, 39, 41, 48-51, and 53 are rejected under 35 U.S.C. § 112, second paragraph as allegedly as being indefinite. Applicants respectfully traverse the present rejection for the following reasons.

Claims 37 and 48 are rejected on the basis of the claim limitation "modified human 5T4". The Examiner contends that the claimed 5T4 cannot be modified and human at the same time. Applicants disagree. The claims have been revised to recite that "the modified human 5T4 antigen is a peptide fragment between 5 and 25 amino acids in length". The specification defines a modified 5T4 antigen as a 5T4 polypeptide which has been truncated, extended, or otherwise mutated such that it differs from naturally-occurring 5T4. See specification, for example, at page 5, lines 22-26. The specification describes 13 examples of human 5T4 peptide fragments in SEQ ID NOS: 5-17, and Examples 10 and 11. Therefore, it is clear what is claimed. The claims are directed to human 5T4 peptide fragments which are between 5 and 25 amino acids in length. The remaining claims depend from either claim 37 or 48 such that the above arguments apply to the dependent claims also. Accordingly, this rejection should be withdrawn.

A substitute specification is enclosed herewith in clean and marked up versions per the request of the Examiner in the Interview of July 10, 2007 (see above). Applicants submit that the substitute specification includes no new matter.

Any cancellation of claimed subject matter herein is done so without prejudice or disclaimer as Applicants reserve the right to pursue such subject matter in a later filed application.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,

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